Status of the Claims

Claim 1 has been amended to delete the term "prevention" and to delete the non-elected diseases or disorders.

Claim 2 has been amended to delete the non-elected diseases or disorders.

Claim 4 has been amended to correct the grammar as suggested by the Examiner.

Claims 1-8 are pending. Claims 9 and 10 have been withdrawn.

Restriction requirement

Applicants acknowledge that the Examiner has made Final the restriction requirement and rejoined method of treating traumatic brain injury or Subarachnoid hemorrhage.

Claim Objections

The Examiner objected to Claim 4 as being grammatically awkward.

Applicants have amended Claim 4 as suggested by the Examiner.

Rejections under 35 U.S.C. 122, first paragraph

I. Prevention

The Examiner rejected Claims 1-8 under 35 U.S.C. 112, first paragraph, because allegedly the specification, while being enabling for treating inhibited growth related disorders (non-elected, which hGH is known to be used for) using a compound of formula I, does not reasonably provide enablement for preventing traumatic brain injury or subarachnoid hemorrhage, using the present compound.

Without acquiescing to the rejection or the reasoning underlying the rejection to facilitate prosecution applicant has amended the claims to delete "prevention". In view of the amendment to the claims it is submitted that the rejection is moot.

II. Treatment

The Examiner rejected Claims 1-8 under 35 U.S.C. 112, first paragraph, because allegedly the specification, while being enabling for treating inhibited growth related disorders (non-elected, which hGH is known to be used for) using a compound of formula I; does not reasonably provide enablement for treating traumatic brain injury or subarachnoid hemorrhage, using the present compound formula I compound.

The Examiner freely concedes that a very broad search of the prior art (EAST) database for the use of hGH in the same paragraph as traumatic brain injury or subarachnoid hemorrhage, *using the present compound formula 1 compound*, yielded only Applicant's present published specification.

The Examiner alleges a search of hGH even **anywhere** in the same reference with traumatic brain injury or subarachnoid hemorrhage produced **no connection** between the two, or enabled specification using hGH for the treatment of either or even a reasonable assertion thereto. The Examiner alleges both the specification and prior art of record lack any reasonable basis as to whether hGH can treat either traumatic brain injury or subarachnoid hemorrhage.

Applicant respectfully submits the Office has failed to establish a *prima facie* case because the prior art of record does provide as a reasonable basis as to whether the claimed conjugates can be used to treat traumatic brain injury and/or subarachnoid hemorrhage. Recognition of pituitary hormonal insufficiencies after head injury and aneurysmal subarachnoid hemorrhage, which may be alleviated by native hGH replacement is known in the art of record [**C10** of IDS filed August 23, 2006 (Kelly, D.F., *J. Neurosurg* 93:743-572,

2000 Hypopituitarism following traumatic brain injury and aneurismal Subarachnoid hemorrhage: a preliminary report)]. Kelly et al. concludes: "*some degree of hypopituitarism appears to occur in approximately 40% of patients with moderate to severe head injury, with GH and gonadotropin deficiencies being most common. . . . The neurobehavioral effects of GH replacement in patients suffering from head injury or SAH warrant further study.*" (p. 743 Abstract) Kelly et al. clearly establishes a connection between traumatic brain injury and subarachnoid hemorrhage and suggests hGH treatment. This initial finding of Kelly et al. is corroborated by numerous other studies of the record [**C8** Aimaretti, G., et al., Residual Pituitary Function after Brain Injury-Induced Hypopituitarism: A Prospective 12-Month Study, *The Journal of Clinical Endocrinology & Metabolism*, 90(11) 6085-6092,2005; **C9** Aimaretti, G., et al., Traumatic Brain Injury and Subarachnoid Haemorrhage are Conditions at High Risk for Hypopituitarism: Screening Study at Three Months after the Brain Injury, *Clinical Endocrinology*, 61: 320-326, 2004; **C11** Kreitschmann-Andermahr, I., et al., Prevalence of Pituitary Deficiency in Patients after Aneurysmal Subarachnoid Hemorrhage, *The Journal of Clinical Endocrinology & Metabolism*, 89(10) 4986-4992, 2004]. In addition to Kelly et al., the connection between traumatic brain injury and subarachnoid hemorrhage and hGH is well established in the prior art. Lieberman et al (*J. Clinical Endocrinology and Metabolism* 86: 2752-2756, 2001 Prevalence of Neuroendocrine Dysfunction in Patients Recovering from Traumatic Brain Injury – submitted herewith in a Supplemental IDS). Lieberman et al. concludes: "*In summary, pituitary hormone deficiencies were identified in a substantial proportion of patients with previous brain injury. GH deficiency, found in 15% by glucagon stimulation testing, may compound the physical and psychological complications of traumatic brain injury and interfere with rehabilitation.*" (Abstract p 2752) The post filing art is replete with corroborative studies on the connection between traumatic brain injury and subarachnoid hemorrhage and hGH.

The prior art also discloses the use of hGH in treating traumatic brain injury (Rockich et al. *Pharmacotherapy* (1999), 19: 1432-6 Effect of recombinant human growth hormone and insulin-like growth factor-1 administration on IGF-1 and IGF-binding protein-3 levels in brain injury – submitted herewith in a Supplemental IDS). Rockich et al. concludes *"infusion*

of rhIGF-1 in conjunction with rhGH effectively achieved and maintained supraphysiologic IGF-1 plasma concentrations throughout the dosing period in patients with TBI." (Abstract p 1432). Yamamura et al evaluated the safety of GH in head trauma patients, by investigating whether GH affects brain oedema caused by brain injury, using a rat freeze-injury model (*Brian Injury* 14: 669-76, 2000, Effect of growth hormone on brain oedema caused by a cryogenic brain injury model in rats submitted herewith in a Supplemental IDS). The post filing art is also replete with corroborative studies on the use of hGH in treating traumatic brain injury. Hatton et al concludes: *"The combination of IGF-I and GH produced sustained improvement in metabolic and nutritional end-points after moderate to severe acute TBI."* (Abstract p. 843 [*Journal of Neurosurgery* (2006), 105: 843-852 Systemic metabolic effects of combined insulin-like growth factor-I and growth hormone therapy in patients who have sustained acute traumatic brain injury, submitted herewith in a Supplemental IDS]) Therefore, contrary to the Examiner's allegation the connection between traumatic brain injury and subarachnoid hemorrhage and hGH was well established in the art.

Section 2107.03 of the MPEP states:

> *As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).*

Therefore, contrary to the Examiner's allegation a reasonable correlation between traumatic brain injury and subarachnoid hemorrhage and hGH is well established in the art.

B. Information Disclosure Statement

A Supplemental Information Disclosure Statement is submitted herewith.

Conclusion

In view of the foregoing, it is respectfully submitted that all claims now pending in the present application are in condition for allowance. Therefore, passage of the application and claims to issue is respectfully requested.

Respectfully submitted,

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